A hydrophilic implantable medical device is disclosed. The device comprises a base material comprising a surface, at least a portion of which comprises a coating comprising a top surface and a bottom surface and at least one layer, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been morphologically and/or chemically modified. The device is fabricated from an orthopedic medical implant in particular, these modifications yield surfaces that exhibit enhanced wettability and lubricity at articular interfaces or enhanced capability for cell attachment at non-articular bone/implant interfaces, as well as the capability for functionalization of the implant surface with biologically active agents.
IMPLANTABLE MEDICAL DEVICES HAVING
HYDROPHILIC SURFACES

GOVERNMENT FUNDING

[0001] This invention was made with government support under Grant No. DE-AC07-05ID14517, awarded by the Department of Energy. The Government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATION

[0002] The present application claims priority benefit to a provisional patent application entitled "Implantable Medical Devices Having Hydrophilic Surfaces," that was filed with the U.S. Patent Office on October 27, 2016, and assigned Serial No. 62/413,723. The entire content of the foregoing provisional application is incorporated herein by reference.

TECHNICAL FIELD

[0003] The present disclosure relates to both orthopedic and non-orthopedic implantable, coated, medical devices, wherein the coating has been modified to increase its hydrophilicity and/or decrease its coefficient of friction or to increase its bone affinity and attachment.

BACKGROUND

[0004] Orthopedic prosthetic implants have been commonly fabricated, at least in part, from alloys based on cobalt-chromium (CoCr) thanks to their outstanding tribological properties, higher hardness, and elastic modulus compared to other materials, such as titanium and titanium-based alloys. In particular, CoCr alloys are preferred over other metals.
and metal alloys, such as titanium, titanium alloys, and stainless steel, to fabricate those portions of orthopedic implants which form part of the articular interface due to the relatively higher resistance of these alloys to wear. For example, many cemented and non-cemented hip prosthetic implants combine a titanium (Ti) or titanium alloy stem for fixation in bone interfaced with a separate CoCr alloy femoral head attached to the fixation stem at a tapered trunion.

[0005] However, despite these desirable attributes, CoCr alloys also have drawbacks to their use in orthopedic implants. First and foremost, CoCr alloys have a well-known biocompatibility problem. Second, as is the case with all metal- and metal alloy-based materials used to fabricate orthopedic implants, CoCr alloys are not particularly hydrophilic and, thus, cannot maintain a degree of lubricity between opposing surfaces of the articular interface comparable to that of native cartilage covered surfaces in a healthy hip joint.

[0006] With regard to biocompatibility, CoCr alloy-based implants have been recognized to cause metallosis in some patients due to cobalt (and chromium) ion buildup in the patient’s body over time. For example, in "metal-on-metal" ("MoM") orthopedic implants (i.e., where the articular interface is formed between two metal- and/or alloy-based implants), corrosion and friction creates particles of metal, metal alloy, metal oxide, and metal alloy oxide in the joint. Corrosion and friction at the CoCr alloy head/Ti stem interface in the above-mentioned hip implants can also create such particles. Cobalt and chromium ions generated from these particles then leach into surrounding tissue and into the bloodstream. A build-up of these ions locally and systemically can result in damage to and necrosis of the tissue and bone surrounding the joint, damage to the muscular, nervous, and cardiovascular systems of the patient, as well as other potentially life-threatening consequences.
This biocompatibility issue can be obviated by substituting titanium or titanium alloys for the CoCr alloy in implants. However, the tribological inferiority of Ti and Ti alloys compared to CoCr requires that it be coated with a ceramic, such as titanium aluminum nitride, to harden the surface of the implant and improve its resistance to wear. While the use of ceramic-coated titanium or titanium alloy in implants might solve the biocompatibility issue of CoCr, it does nothing to mitigate its inability to maintain lubricity in the articular interface comparable to natural hip joints, since, like metals and metal alloys, the surfaces of the ceramics used in such coatings are also not particularly hydrophilic.

Accordingly, there exists a continuing need for improved orthopedic implants possessing both superior biocompatibility compared to CoCr-based implants and a superior ability to maintain adequate lubricity at the articular interface compared to metal-, metal alloy-, and ceramic-coated metal-based implants. Ideally, these improvements are the result of engineered modulation of the surface energy of the implant, such as by functionalization of the implant surface with hydrophilic groups (e.g., hydroxyl or oxide groups) or by imparting morphological changes, such as micropores, nanopores, or dimples, to the surface of the implant. Such modulation of the surface energy of the implant enhances wettability and lubricity of its surface against native cartilage and hydrophobic surfaces, such as ceramic coatings and polymers (e.g., UHMWPE), or can provide for enhanced capability for cell attachment at non-articular bone/implant interfaces, as well as the capability for functionalization of the implant surface with biologically active agents. The present disclosure provides for such improved orthopedic implants, as well as for improved implantable medical devices in general having such advantages.
SUMMARY

[0009] One embodiment of the present invention relates to an implantable medical device comprising a base material comprising a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and one or more layers, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits increased hydrophilicity relative to the hydrophilicity of the at least a portion of the coating prior to modification.

[0010] Another embodiment of the present invention relates to an implantable medical device comprising a base material comprising a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and at least one layer, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits a decreased coefficient of friction relative to the coefficient of friction of the at least a portion of the coating prior to modification.

[0011] Yet another embodiment of the present invention relates to an implantable medical device comprising a base material comprising a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and at least one layer, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits increased bone affinity and attachment relative to the bone affinity and attachment of at least a portion of the coating prior to modification.
The present invention may be implemented by way of embodiments that include one or more of the following features.

In exemplary embodiments, the disclosed coating can comprise a surface layer and at least one intermediate layer disposed between the surface layer and the surface of the base material. In certain embodiments, the coating can comprise from 1 to 12 intermediate layers. In certain embodiments, the at least one intermediate layer is a bonding layer. In certain embodiments, the bonding layer of the coating interfaces with the surface of the base material. In certain embodiments, the hydrophilic portion of the coating comprises hydroxyl groups. In certain embodiments, the hydrophilic portion of the coating comprises oxide groups. In certain embodiments, the hydrophilic portion of the coating comprises micropores, nanopores, etches, surface texturing/patterning, and/or dimples.

In exemplary embodiments, the base material can comprise a material selected from the group consisting of metals, metal alloys, ceramics, polymers, silicon-based compounds, metal matrix composites, ceramic matrix composites, polymer matrix composites, and combinations thereof. In certain embodiments, the base material can comprise a metal selected from the group consisting of titanium, titanium alloys, cobalt, cobalt alloys, cobalt-chromium alloys, tantalum, tantalum alloys, niobium, niobium alloys, zirconium, zirconium alloys, stainless steel, and combinations thereof. In those embodiments, the metal may further comprise a dopant. In certain embodiments, the dopant can be selected from the group consisting of alkaline earth metals, transition metals, and rare earth metals. In certain embodiments, the dopant can be selected from the group consisting of calcium, magnesium, strontium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, zirconium, and niobium. In certain other embodiments, the base material can comprise a polymer selected from the group consisting of ultrahigh molecular
weight polyethylene, polyethylene oxide, polypropylene, polytetrafluoroethylene, polylactic acid, polyglycol acid, copolymers of polylactic acid and polyglycol acid, and combinations thereof. In certain other embodiments, the base material can comprise a ceramic of formula (I):

\[
[(\text{Mi})_a (\text{M}_2)_b (\text{M}_3)_c x[(0)_d (\text{C})_e (\text{N})_f]^{i,x})
\]

wherein \(\text{Mi}, \text{M}_2,\) and \(\text{M}_3\) are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B; O is oxygen; C is carbon; N is nitrogen; \(a, b, c, d, e,\) and \(f\) are each a number in the range of from 0 to 1, with the proviso that the sum of \(a, b,\) and \(c\) is equal to 1 and the sum of \(d, e,\) and \(f\) is equal to 1; and \(x\) is a number greater than 0 and less than 1.

[0015] In exemplary embodiments, the base material can comprise a ceramic selected from the group consisting of titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof.
In exemplary embodiments, the coating can comprise a material selected from the group consisting of ceramics, metals, metal alloys, and combinations thereof. In certain embodiments, the coating can comprise a ceramic of formula (I):

\[ \left( M_1^{a_1} M_2^{b_2} M_3^{c_3} \right) \left( O \right)_{d} \left( C \right)_{e} \left( N \right)_{f} \]  

(1)

wherein \( M_1, M_2, \) and \( M_3 \) are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B; O is oxygen; C is carbon; N is nitrogen; \( a, b, c, d, e, \) and \( f \) are each a number in the range of from 0 to 1, with the proviso that the sum of \( a, b, \) and \( c \) is equal to 1 and the sum of \( d, e, \) and \( f \) is equal to 1; and \( x \) is a number greater than 0 and less than 1.

In exemplary embodiments, the base material can comprise a ceramic selected from the group consisting of titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof. In certain embodiments, the coating can have a thickness in the range of from 0.5 μη to 20 μη, and in other exemplary embodiments, the coating can
have a thickness in the range of from 0.5 µη to 15 µη. In certain embodiments, the coating can be applied to the surface of the base material via physical vapor deposition (PVD), cathodic arc PVD, steered cathodic arc PVD, filtered cathodic arc PVD, plasma-assisted PVD, laser-assisted PVD, DC magnetron sputtering, RF magnetron sputtering, unbalanced magnetron sputtering, high power impulse magnetron sputtering, chemical vapor deposition (CVD), plasma-assisted CVD, laser-assisted CVD, plasma-enhanced CVD, photo-enhanced CVD, metal-organic CVD, atmospheric pressure CVD, ion plating, pulsed laser deposition, atomic laser deposition, cold spray, thermal spray, solution plasma spray, solution precursor plasma spray, plating, reactive evaporation, reactive ion beam assisted deposition, and combinations or hybrid techniques thereof.

[0019] In exemplary embodiments, a biologically active agent may be incorporated into and/or onto the coating. In certain embodiments, the biologically active agent may be hydrogen bonded to the coating. In certain of those embodiments, the biologically active agent is hydrogen bonded to the coating via one or more hydroxyl groups. In certain embodiments, the biologically active agent may be covalently bonded to the coating. In certain of those embodiments, the biologically active agent may be covalently bonded to the coating via one or more hydroxyl groups. In certain embodiments, the biologically active agent can be selected from the group consisting of proteins, peptides, aptamers, standard and non-standard amino acids, lipids, lipopolysaccharides, growth factors, cytostatic agents, hormones, antibiotics, anti-microbial agents, anti-allergenic agents, steroidal and non-steroidal anti-inflammatory agents, progestational agents, humoral agents, antipyretic agents, osteoinductive agents, osteoconductive agents, pro-osteogenic compounds, and combinations thereof.
In exemplary embodiments, the implantable medical device can be an orthopedic implantable medical device. In certain embodiments, the orthopedic implantable medical device may be selected from the group consisting of bone caps, plates, cerclages, rods, dowels, pegs, smooth fasteners, threaded fasteners, screws, staples, nails, washers, nuts, bolts, clamps, fixation orthoses, pedicle screw systems intervertebral body fusion devices, ankle joint prostheses, elbow joint prostheses, hinged elbow fixators, finger joint prostheses, hip joint prostheses, knee joint femorotibial prostheses, knee joint patellofemoral prostheses, knee joint patellofemorotibial prostheses, knee joint femoral prostheses, knee joint patellar prostheses, knee joint tibial prostheses, shoulder joint prostheses, wrist joint prostheses, maxillofacial prostheses, cranial prostheses, pelvic fixators, cranial distractors, transmandibular implants, mandibular fixators and distractors, preformed cement bone replacements, polymer bone replacements, and orthodontic prostheses. In certain embodiments, the base material of the orthopedic implantable medical device can comprise titanium metal or an alloy thereof. In certain embodiments, the coating of the orthopedic implantable device can comprise at least one layer comprising a ceramic of formula (II):

\[ \text{Ti}_x\text{Al}_{(1-x)}\text{N} \] (II)

wherein \(x\) is a number greater than 0 and less than 1. In certain of those embodiments, the at least one layer of a ceramic of formula (II) can have an aluminum concentration of up to 80% by weight. In certain of those embodiments, the concentration of aluminum in the at least one layer of a ceramic of formula (II) can increase in a gradient from the surface of at least one layer disposed closest to the surface of the base material to the surface of at least one layer disposed furthest from the surface of the base material. In certain embodiments, the coating can be located on a surface of the orthopedic implantable medical device that interfaces with bone. In certain embodiments, the coating can be located on a surface of the
orthopedic implantable medical device that forms an articulating interface when implanted. In certain embodiments, the orthopedic implantable medical device can be a hip joint prosthesis having a femoral head with the coating located on the femoral head. In certain embodiments, the coating can be located on the surface of the implantable medical device that attaches to or interfaces with tissue when implanted.

[0021] In exemplary embodiments, the implantable medical device can be a non-orthopedic medical device. In certain embodiments, the non-orthopedic implant can be selected from the group consisting of cardiac pacemakers, heart valve rotators, esophageal prostheses, smooth fasteners, threaded fasteners, sacculotomy tacks, clips, nerve stimulators, ocular orbital implants, shunts and shunt tubes, fistula adapters, cardiac event recorders, stents, ports, tympanostomy tubes, eyelid weights, prostate magnetic and thermal rod systems, surgical meshes, tracheostomy tubes and tube cuffs, tracheal prostheses, in utero fetal tracheal occlusion devices, tongue suspension systems, defibrillators, ionizing radiation dosimeters, radio frequency transponder systems, aneurysm pressure sensors, catheters, uterine implants, mitral valve prostheses, hearing aids, and orbital tissue expanders.

[0022] In exemplary embodiments, at least a portion of the coating can be modified by (1) exposing the coating to ozone, (2) exposing the coating to water or steam at a temperature above ambient temperature, (3) exposing the coating to a basic solution at a temperature above ambient temperature, or (4) altering the surface morphology of the coating and optionally coating the morphologically altered coating with a polymer or wax, or (5) any combination thereof. In certain embodiments, the exposure of (1), (2), (3) and (4) can be conducted for a time period in the range of from 1 minute to 168 hours. In certain embodiments, the exposure of (1), (2), (3) and (4) can be conducted at a pressure above atmospheric pressure. In certain embodiments, the basic solution can be selected from the
group consisting of aqueous solutions comprising NaOH, aqueous solutions comprising
KOH, aqueous solutions comprising Ca(OH)2, aqueous solutions comprising Mg(OH)2, and
any combination thereof. In certain embodiments, the hydrophilicity of the coating can be
increased by 0.001 to 1000%, relative to the hydrophilicity of the coating prior to
modification. In certain embodiments, the coefficient of friction of the coating can be
decreased by 0.001 to 99.999%, relative to the coefficient of friction of the coating prior to
modification.

[0023] Additional features, functions and benefits of the present invention will be
apparent from the description of exemplary embodiments which follows.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0024] In this application, the use of the singular includes the plural unless
specifically stated otherwise. In this application, the use of "or" means "and/or" unless stated
otherwise. Furthermore, the use of the term "including," as well as other forms, such as
"includes" and "included," is not limiting. Any ranges described herein will be understood to
include the endpoints and all values between the endpoints.

[0025] Any section headings used herein are for organizational purposes only and are
not to be construed as limiting the subject matter described. All documents, or portions of
documents, cited in this application, including, but not limited to, patents, patent applications,
articles, books, and treatises, are hereby expressly incorporated by reference in their entirety
for any purpose.

[0026] In various aspects, configurations and embodiments, the present disclosure
provides for implantable medical devices having a surface coating that has been modified to
increase its hydrophilicity and/or decrease its coefficient of friction or to increase its bone affinity and attachment. The presently disclosed implantable medical devices comprise a base material comprising a surface, wherein at least a portion of the surface of the base material comprises a coating. The coating comprises a top surface, a bottom surface, and one or more layers. The bottom surface interfaces with the surface of the base material, while at least a portion of the top surface has been modified such that it exhibits increased hydrophilicity and/or decreased coefficient of friction or increased bone affinity and attachment relative to the hydrophilicity and/or coefficient of friction or bone affinity and attachment of the at least a portion of the coating prior to modification.

[0027] As used herein, the term "implantable medical device" encompasses any device, instrument, apparatus, appliance, implant, material, or other article that can be implanted into the body of a mammal to treat, alleviate, prevent, compensate for, monitor, and/or diagnose a disease, injury, or handicap or to replace and/or modify a part of the anatomy or a physiological process of the mammal. In certain embodiments, the mammal is a human. In certain embodiments, the presently disclosed implantable medical device can be any non-absorbable medical device classified as implantable by the Food and Drug Administration. In certain embodiments, the presently disclosed implantable medical device can be any orthopedic medical device. Examples of such orthopedic medical devices include, but are not limited to, bone caps, plates, including bone growth control plates, cerclages, rods (e.g., intramedullary fixation rods), dowels, pegs, smooth fasteners, threaded fasteners, including screws (e.g., spinal facet screws), staples, nails (e.g., femoral nails), washers, nuts, bolts, clamps, fixation orthoses, including spinal interlaminar fixation orthoses and spinal intervertebral body fixation orthoses, pedicle screw systems, intervertebral body fusion devices, ankle joint prostheses, including subtalar prostheses, elbow joint prostheses,
including radial prostheses and humeral prostheses, hinged elbow fixators, finger joint prostheses, hip joint prostheses, including femoral prostheses, acetabular prostheses, and femoral trunnion-bearing prostheses, knee joint femorotibial prostheses, knee joint patellofemoral prostheses, knee joint patellofemoro tibial prostheses, knee joint femoral prostheses, knee joint patellar prostheses, knee joint tibial prostheses, shoulder joint prostheses, including glenoid prostheses and humeral prostheses, toe joint prostheses, including metatarsophalangeal and phalangeal prostheses, wrist joint prostheses, including carpal lunate prostheses, carpal scaphoid prostheses, carpal trapezium prostheses, and ulnar prostheses, maxillofacial prostheses, including malar prostheses, cranial prostheses (e.g., temporal prostheses), pelvic fixators, cranial distractors, transmandibular implants, mandibular fixators and distractors, preformed cement bone replacements, polymer bone replacements, and orthodontic prostheses. In certain embodiments, the presently disclosed implantable medical device can be any non-orthopedic medical device. Examples of such non-orthopedic medical devices include, but are not limited to, cardiac pacemakers, heart valve rotators, esophageal prostheses, smooth or threaded fasteners, including sutures, staples, and clamps, ocular pegs, sacculotomy tacks, clips, including venous and vena cava clips, nerve stimulators, including spinal cord, peripheral, and vagus nerve stimulators, ocular orbital implants, shunts and shunt tubes, including peritoneal shunts, central nervous system shunts, arteriovenous (AV) shunts, and endolymphatic shunt tubes, fistula adapters, cardiac event recorders, stents, including ureteral stents, lacrimal stents, internal pudendal artery stents, colonic stents, duodenal stents, and tibial arterial stents, ports, tympanostomy tubes, eyelid weights, prostate magnetic and thermal rod systems, surgical meshes, such abdominal wall meshes, urogynecological meshes, diaphragmatic hernia meshes, tendon reinforcement meshes, thoracic/chest wall reconstruction meshes, staple line reinforcement meshes, and plastic/reconstructive surgery meshes, tracheostomy tubes and tube cuffs, tracheal prostheses,
in utero fetal tracheal occlusion devices, tongue suspension systems, defibrillators, ionizing radiation dosimeters, radio frequency (RF) transponder systems, aneurysm pressure sensors, catheters, uterine implants, mitral valve prostheses, including annuloplasty rings, hearing aids, and orbital tissue expanders.

[0028] As used herein, the phrase "base material" is defined as the material at the surface or surfaces of the presently disclosed implantable medical devices that interface with the bottom surface of the coating. However, it is to be understood from the present disclosure that, in certain embodiments, other portions of or substantially all of the presently disclosed implantable medical devices may also comprise the same material as the base material or, alternatively, a material that is different from the base material. The base material of the presently disclosed implantable medical devices can comprise any known biocompatible material suitable for implantation into a mammal, such as a human. Such suitable biocompatible materials include, but are not limited to, certain metals, metal alloys, ceramics, polymers, silicon-based compounds, metal matrix composites, ceramic matrix composites, polymer matrix composites, and combinations thereof. As used herein, the terms "metal matrix composite," "ceramic matrix composite," and "polymer matrix composite" are each defined as a composite material made from two or more constituent materials, one of which is a metal, ceramic, or polymer, respectively, that is the continuous phase in which the other constituent materials (e.g., a reinforcing material) is/are embedded.

[0029] Examples of suitable biocompatible metals that can form, in whole or in part, the base material of the presently disclosed implantable medical devices include, but are not limited to, titanium, titanium alloys, cobalt, cobalt alloys, cobalt-chromium-based alloys, tantalum, tantalum alloys, niobium, niobium alloys, zirconium, zirconium alloys, stainless steel, and combinations thereof. In certain embodiments, the base material is titanium metal
or an alloy thereof. In certain embodiments, these metals may be doped with one or more
dopants. Suitable dopants may include an alkaline earth metal, a transition metal, and/or a
rare earth element. Examples of suitable dopants include, but are not limited to, calcium,
magnesium, strontium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel,
copper, zinc, zirconium, and niobium.

[0030] Examples of suitable biocompatible polymers that can form, in whole or in
part, the base material of the presently disclosed implantable medical devices include, but are
not limited to, ultrahigh molecular weight polyethylene (i.e., UHMWPE), polyethylene oxide
(i.e., PEO), polypropylene (i.e., PPO), polytetrafluoroethylene (i.e., PTFE), polylactic acid
(i.e., PLA), polyglycol acid (i.e., PGA), copolymers of polylactic acid and polyglycol acid,
and combinations thereof.

[0031] An example of a suitable biocompatible silicon-based compounds that can
form, in whole or in part, the base material of the presently disclosed implantable medical
devices includes, but is not limited to, silicone elastomers such as silastic.

[0032] An example of a suitable polymer matrix composite that can form, in whole or
in part, the base material of the presently disclosed implantable medical devices includes, but
is not limited to, carbon fiber composites, where carbon fibers are embedded in a polymeric
continuous phase.

[0033] Suitable biocompatible ceramics that can form, in whole or in part, the base
material of the presently disclosed implantable medical devices include ceramics of
formula (I):

\[
[(\text{Mi})_a(\text{M}_2)_b(\text{M}_3)_c]_x[0]_d(C)e(N)f(\text{i-x}) \quad (1)
\]
wherein $M_1$, $M_2$, and $M_3$ are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B; $O$ is oxygen; $C$ is carbon; $N$ is nitrogen; $a$, $b$, $c$, $d$, $e$, and $f$ are each a number in the range of from 0 to 1, with the proviso that the sum of $a$, $b$, and $c$ is equal to 1 and the sum of $d$, $e$, and $f$ is equal to 1; and $x$ is a number greater than 0 and less than 1. Examples of such biocompatible ceramics include, but are not limited to, titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof.

[0034] As used herein, the term "coating" is defined as at least one layer of one or more biocompatible materials that has been applied to and adheres to at least a portion of the surface of the base material of the presently disclosed implantable medical devices such that it covers the surface of the base material to which it is adhered. The coating of the presently disclosed implantable medical devices can be fabricated from and, thus, comprise any known biocompatible material suitable for implantation in a mammal. Such suitable biocompatible materials include, but are not limited to, certain ceramics, metals, and combinations thereof. Examples of suitable biocompatible metals that can form, in whole or in part, the coating of
the presently disclosed implanted medical devices include, but are not limited to, titanium, titanium alloys, cobalt, cobalt alloys, cobalt-chromium-based alloys, tantalum, tantalum alloys, niobium, niobium alloys, zirconium, zirconium alloys, stainless steel, and combinations thereof. Suitable biocompatible ceramics that can form, in whole or in part, the coating of the presently disclosed implanted medical devices include ceramics of formula (I):

$$[(M_1)_a(M_2)_b(M_3)_c][O]_d(C)_e(N)_f]^{(1-x)}$$

wherein $M_1$, $M_2$, and $M_3$ are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B; O is oxygen; C is carbon; N is nitrogen; a, b, c, d, e, and f are each a number in the range of from 0 to 1, with the proviso that the sum of a, b, and c is equal to 1 and the sum of d, e, and f is equal to 1; and $x$ is a number greater than 0 and less than 1. Examples of such biocompatible ceramics include, but are not limited to, titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof.
In exemplary embodiments, the coating of the presently disclosed implantable medical devices is a single layer of biocompatible material. In certain other embodiments, the coating of the presently disclosed implantable medical devices is composed of two or more layers of biocompatible material, *i.e.*, applying a first layer of biocompatible material to the surface of the base material, followed by successively applying one or more subsequent layers of biocompatible material to the top surface of the previous layer of biocompatible material. In those embodiments where the coating of the presently disclosed implantable medical devices is composed of two or more individual layers of biocompatible material, the biocompatible material of each individual layer may be the same or different, or the biocompatible material of certain individual layers is the same while that of certain other individual layers is different. In certain embodiments, the coating of the presently disclosed biocompatible medical devices can comprise a surface layer and at least one intermediate layer disposed between the surface layer and the surface of the base material. In certain embodiments, the coating can comprise from 1 to 12 intermediate layers. In certain embodiments, at least one of these intermediate layers is a bonding layer. In certain embodiments, the bonding layer of the coating interfaces with the surface of the base material.

In exemplary embodiments, the presently disclosed implantable medical devices can be fabricated by (1) applying one or more layers comprising one or more biocompatible materials to at least a portion of the surface of the base material of an implantable medical device so as to form a coating, followed by (2) exposing at least a portion of the coating to physical conditions and/or chemical reagents such that the at least a portion of the coating is modified so that the coating exhibits (1) increased hydrophilicity and/or (2) a decreased coefficient of friction or (3) an increased bone affinity and attachment
relative to the coating prior to such modification. In certain embodiments, the at least a portion of the coating is morphologically modified to comprise micropores, nanopores, etches, surface texturing/patterning and/or dimples. In certain embodiments, the at least a portion of the coating is chemically modified to comprise functional groups. As used herein, the phrase "functional group" encompasses any functional group (i.e., hydroxyl, oxide, carboxylate, amino, etc.) capable of imparting increased hydrophilicity and/or a decreased coefficient of friction or an increased bone affinity and attachment to the presently disclosed coatings. In certain embodiments, the surface layer is functionalized with hydroxyl groups and/or oxide groups. The presence of such morphological modifications and/or functional groups on at least a portion of the coating can modulate the surface energy of the implant such that the wettability and lubricity of the implant surface against native cartilage and hydrophobic surfaces, such as ceramic coatings and polymers (e.g., UHMWPE), is enhanced, and also enhances cell attachment capability at non-articular bone/implant interfaces, as well as the capability for functionalization of the implant surface with biologically active agents.

[0037] The one or more layers comprising one or more biocompatible materials that form the coating on the surface of the base material can be applied to the base material by any known technique. Examples of such techniques include, but are not limited to, physical vapor deposition (PVD), cathodic arc PVD, steered cathodic arc PVD, filtered cathodic arc PVD, plasma-assisted PVD, laser-assisted PVD, DC magnetron sputtering, RF magnetron sputtering, unbalanced magnetron sputtering, high power impulse magnetron sputtering, chemical vapor deposition (CVD), plasma-assisted CVD, laser-assisted CVD, plasma-enhanced CVD, photo-enhanced CVD, metal-organic CVD, atmospheric pressure CVD, ion plating, pulsed laser deposition, atomic laser deposition, cold spray, thermal spray, solution plasma spray, solution precursor plasma spray, plating, reactive evaporation, and reactive ion
beam assisted deposition. Any combination or hybrid of two or more of these techniques may be used.

[0038] The coating can be of any useful total thickness. In certain embodiments, the total thickness of the coating can be any thickness in the range of from 0.001 µm to 100 µm. In certain embodiments, the total thickness of the surface layer can be any thickness in the range of from 0.005 µm to 20 µm. In certain embodiments, the total thickness of the surface layer can be any thickness in the range of from 0.5 µm to 15 µm. Examples of such thicknesses include, but are not limited to, 0.0001 µm, 0.0005 µm, 0.001 µm, 0.005 µm, 0.01 µm, 0.015 µm, 0.02 µm, 0.025 µm, 0.03 µm, 0.035 µm, 0.04 µm, 0.045 µm, 0.05 µm, 0.055 µm, 0.06 µm, 0.065 µm, 0.07 µm, 0.08 µm, 0.09 µm, 0.1 µm, 0.15 µm, 0.2 µm, 0.25 µm, 0.3 µm, 0.35 µm, 0.4 µm, 0.45 µm, 0.5 µm, 0.55 µm, 0.6 µm, 0.65 µm, 0.7 µm, 0.75 µm, 0.8 µm, 0.85 µm, 0.9 µm, 0.95 µm, 1.0 µm, 1.5 µm, 2.0 µm, 2.5 µm, 3.0 µm, 3.5 µm, 4.0 µm, 4.5 µm, 5.0 µm, 5.5 µm, 6.0 µm, 6.5 µm, 7.0 µm, 7.5 µm, 8.0 µm, 8.5 µm, 9.0 µm, 9.5 µm, 10.0 µm, 10.5 µm, 11.0 µm, 11.5 µm, 12.0 µm, 12.5 µm, 13.0 µm, 13.5 µm, 14.0 µm, 14.5 µm, 15.0 µm, 15.5 µm, 16.0 µm, 16.5 µm, 17.0 µm, 17.5 µm, 18.0 µm, 18.5 µm, 19.0 µm, 19.5 µm, and 20.0 µm. In those certain embodiments where the coating comprises two or more individual layers, each individual layer can be of any thickness such that, in the aggregate, the coating is of any useful total thickness. In certain embodiments, the thickness of each individual layer can be any thickness less than 100 µm. In certain embodiments, the thickness of each individual layer can be any thickness less than 20 µm. In certain embodiments, the thickness of each individual layer can be any thickness less than 15 µm. Examples of thicknesses for individual layers include, but are not limited to, 0.0001 µm, 0.0005 µm, 0.001 µm, 0.005 µm, 0.01 µm, 0.015 µm, 0.02 µm, 0.025 µm, 0.03 µm, 0.035 µm, 0.04 µm, 0.045 µm, 0.05 µm, 0.055 µm, 0.06 µm, 0.065 µm, 0.07 µm.
The coating can be applied to any surface of an implantable medical device. In certain embodiments, the coating is applied to the surface of an implantable medical device that attaches to or interfaces with tissue. In certain embodiments where the implantable medical device is an orthopedic implantable medical device, the coating can be applied to the surface of the device that interfaces with bone, the surface of the device that, when implanted, forms the articular interface, or both. For example, where the implantable medical device is a hip joint prosthesis, the coating can be applied to the femoral component on the femoral head, the femoral stem, or both the femoral head and femoral stem and/or can be applied to the portion of the acetabular component that interfaces with the pelvic bone, the portion of the acetabular component that forms, in part, the articular interface, or both.

The coating can be modified by exposing it to any physical conditions and/or chemical reagents that can morphologically and/or chemically modify the coating such that it exhibits increased hydrophilicity and/or a decreased coefficient of friction or an increased bone affinity and attachment as a result of such modification. In certain embodiments, the coating is functionalized with hydroxyl groups by exposing it to water or steam at ambient temperature or higher and at atmospheric pressure or higher for a period time. In certain embodiments, the coating is functionalized with hydroxyl groups by exposing it to a base at
ambient temperature or higher and at atmospheric pressure or higher for a period time. In certain embodiments, the base is in the form of a basic solution. In certain embodiments the basic solution is aqueous. In certain embodiments, the base is NaOH, KOH, Ca(OH)$_2$, Mg(OH)$_2$, or a combination thereof. In certain embodiments, the coating is functionalized with oxide groups by exposing it to ozone at ambient temperature or higher and at atmospheric pressure or higher for a period time. In certain embodiments, the coating is morphologically modified to comprise micropores, nanopores, etches, surface texturing/patterning and/or dimples by exposing it to an acid at ambient temperature or higher and at atmospheric pressure or higher for a period time. In certain embodiments, the acid is an acidic solution or a gaseous acid. In certain embodiments the acidic solution is an aqueous acidic solution. In certain embodiments, the acid is HF, HCl, HBr, H$_2$SO$_4$, HNO$_3$, H$_3$PO$_4$, CH$_3$COOH, and CF$_3$COOH, or a combination thereof. In certain embodiments, the coating is exposed to ozone, water, steam, base, or acid at a temperature in the range of from 25 °C to 700 °C. In certain embodiments, the coating is exposed to ozone, water, steam, base, or acid at a temperature in the range of from 100 °C to 500 °C. Examples of such temperatures include, but are not limited to, 100 °C, 110 °C, 120 °C, 130 °C, 140 °C, 150 °C, 160 °C, 170 °C, 180 °C, 190 °C, 200 °C, 210 °C, 220 °C, 230 °C, 240 °C, 250 °C, 260 °C, 270 °C, 280 °C, 290 °C, 300 °C, 310 °C, 320 °C, 330 °C, 340 °C, 350 °C, 360 °C, 370 °C, 380 °C, 390 °C, 400 °C, 410 °C, 420 °C, 430 °C, 440 °C, 450 °C, 460 °C, 470 °C, 480 °C, 490 °C, and 500 °C. In certain embodiments, the coating is exposed to ozone, water, steam, base, or acid at a pressure in the range of from 0.101325 MPa (i.e., 1 atm) to 50 MPa. In certain embodiments, the coating is exposed to ozone, water, steam, base, or acid at a pressure in the range of from 1 MPa to 30 MPa. Examples of such pressure include, but are not limited to, 1 MPa, 2 MPa, 3 MPa, 4 MPa, 5 MPa, 6 MPa, 7 MPa, 8 MPa, 9 MPa, 10 MPa, 11 MPa, 12 MPa, 13 MPa, 14 MPa, 15 MPa, 16 MPa, 17 MPa, 18 MPa, 19 MPa, 20 MPa,
21 MPa, 22 MPa, 23 MPa, 24 MPa, 25 MPa, 26 MPa, 27 MPa, 28 MPa, 29 MPa, and 30 MPa. In certain embodiments, the coating is exposed to ozone, water, steam, base, or acid for a time period in the range of 1 minute to 168 hours. In certain embodiments, the surface layer is exposed to water or steam for a time period in the range of 6 hours to 120 hours. Examples of such times include, but are not limited to, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 16 hours, 20 hours, 24 hours, 30 hours, 36 hours, 42 hours, 48 hours, 54 hours, 60 hours, 66 hours, 72 hours, 78 hours, 84 hours, 90 hours, and 96 hours. Any combination of temperature, pressure, and time sufficient to functionalize the top surface of the surface layer coating with oxide groups, hydroxyl groups, or to morphologically modify the coating may be employed.

[0041] The coating of the presently disclosed implantable medical devices may be exposed to ozone, water, steam, base, or acid in any apparatus capable of withstanding any particular combination of the above temperatures and pressures and/or acidic, basic, or oxidizing conditions for the requisite time period necessary to functionalize or morphologically modify the coating. Examples of such an apparatuses include, but are not limited to, baths, immersion vessels, and autoclaves, such as a static autoclave. Characteristics of the coating post-modification can determined by various analytical techniques including, but not limited to, X-ray diffraction (XRD), optical microscopy (OM), scanning electron microscopy (SEM), and energy dispersive X-ray spectroscopy (EDS).

[0042] In exemplary embodiments, the presently disclosed implantable medical device can be an orthopedic implantable medical device, the base material of which comprises titanium or a titanium alloy. In certain embodiments, the presently disclosed implantable medical device can be an orthopedic implantable medical device, the coating of which comprises aluminum metal, an aluminum-containing alloy, or an aluminum-containing
compound, such as $\text{Al}_3\text{O}_3$, $\text{YAlO}_3$, or $\text{AI}_5\text{LU}_3\text{O}_{12}$. In certain embodiments, the presently disclosed implantable medical device can be an orthopedic implantable medical device, the coating of which comprises at least one layer comprising a ceramic of formula (II):

$$\text{Ti}_x\text{Al}_{(1-x)}\text{N} \quad (\text{II})$$

The titanium and aluminum can be present in the ceramic of formula (II) in any ratio. Thus, "x" has a value greater than zero and less than one. Examples of values for "x" include, but are not limited to, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.31, 0.32, 0.33, 0.34, 0.35, 0.36, 0.37, 0.38, 0.39, 0.40, 0.41, 0.42, 0.43, 0.44, 0.45, 0.46, 0.47, 0.48, 0.49, 0.50, 0.51, 0.52, 0.53, 0.54, 0.55, 0.56, 0.57, 0.58, 0.59, 0.60, 0.61, 0.62, 0.63, 0.64, 0.65, 0.66, 0.67, 0.68, 0.69, 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79, 0.80, 0.81, 0.82, 0.83, 0.84, 0.85, 0.86, 0.87, 0.88, 0.89, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, and 0.99. In certain embodiments, the titanium or aluminum can be present in the ceramic of formula (II) in any total concentration that is greater than 0 % by weight and less than 100 % by weight. In certain embodiments, the titanium and aluminum are present in the ceramic of formula (II) in a ratio of 50%/50% by weight. In certain embodiments, the titanium and aluminum are present in the ceramic of formula (II) in a ratio of 31%/69% by weight. Examples of such titanium or aluminum concentrations include, but are not limited to, concentrations of or up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 % by weight. In certain embodiments, the concentration of either the titanium or the aluminum in the at least one layer comprising the ceramic of
formula (II) can increase or decrease in a gradient from the surface of the at least one layer disposed closest to the surface of the base material to the surface of the at least one layer disposed furthest from the surface of the base material. For example, the concentration of aluminum in the ceramic of formula (II) at the surface of the at least one layer disposed closest to the surface of the base material can increase from 1% by weight steadily to 99% by weight at the surface of the at least one layer disposed furthest from the surface of the base material. In certain other embodiments, the concentration of either the titanium or the aluminum in the at least one layer comprising the ceramic of formula (II) can increase or decrease incrementally from the surface of the at least one layer disposed closest to the surface of the base material to the surface of the at least one layer disposed furthest from the surface of the base material. In certain other embodiments, the at least one layer comprising the ceramic of formula (II) can have different concentrations of either the titanium or the aluminum at different strata of the at least one layer. Such different relative concentrations of titanium and aluminum at various strata within the at least one layer can be achieved by varying the relative amounts of titanium and aluminum during deposition of the at least one layer on the base material.

[0043] In exemplary embodiments, chemical and/or morphological modification of the coatings of the presently disclosed implantable medical devices can result in mineralization of the surface of the coating. For example, when a coating comprising the ceramic of formula (II) is exposed to water, steam, or a hydroxide base at ambient temperature or higher and at atmospheric pressure or higher for a period time, the coating can be functionalized with hydroxyl groups. Without being bound by theory, such exposure can cause the migration of aluminum towards the top surface of the coating, where it oxidizes to form a phase of boehmite, an aluminum oxide hydroxide (γ-AIO(OH)) mineral, over the layer
comprising the now-aluminum-depleted ceramic of formula (II). In embodiments where the surface of such an implantable medical device attaches to or interfaces with tissue, such mineralization can enhance bone growth at the point of attachment or interface.

[0044] Chemical and/or morphological modification of the coatings of the presently disclosed implantable medical devices can result in coatings that exhibit increased hydrophilicity relative to the hydrophilicity of the coating prior to modification. In certain embodiments, the hydrophilicity of the coating can be increased by 0.001 to 1000%, relative to the hydrophilicity of the coating prior to modification. Examples of such increases in relative hydrophilicity include, but are not limited to, 0.001%, 0.01%, 0.1%, 1%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, and 1000%. Chemical and/or morphological modification of the coatings of the presently disclosed implantable medical devices can result in coatings that exhibit a decreased coefficient of friction relative to the coefficient of friction of the coating prior to modification. In certain embodiments, the coefficient of friction of the coating can be increased by 0.001 to 99.999%, relative to the coefficient of friction of the coating prior to modification. Examples of such increases in relative coefficient of friction include, but are not limited to, 0.001%, 0.01%, 0.1%, 1%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.9%, 99.99%, and 99.999%.

[0045] In exemplary embodiments, a biologically active agent can be incorporated into and/or onto the coating of the presently disclosed implantable medical devices. As used herein, the term "biologically active agent" encompasses any compound or composition of matter that exhibits a beneficial and/or adverse effect on living matter. The presently-disclosed biologically active agents can be, for example, a protein, a glycoprotein, a peptide,
a steroid, a small molecule, a lipid, an oligonucleotide, a polynucleotide, or a polymer.

Examples of classes of such biologically active agents include, but are not limited to, standard and non-standard amino acids, lipopolysaccharides, growth factors, cytostatic agents, hormones, anti-microbial agents (e.g., antibiotics, antifungals, antivirals, etc.), anti-allergenic agents, anti-inflammatory agents (steroidal and non-steroidal), progestational agents, and antipyretic agents.

[0046] Specific examples of biologically active agents that may be incorporated into and/or onto the coating of the presently disclosed implantable medical devices include, but are not limited to: 3F8, 5-fluorouracil, 6-mercaptopurine, 6-thioguanine, 8H9, A-349,821, abacavir, abagovomab, abciximab, abituzumab, abrilumab, ABT-239, aceclofenac, acetaminophen (paracetamol), aclarubicin, acrivastine, actinomycin, actoxumab, acyclovir, adalimumab, adecatumumab, adeovir, adiponectin, adrenocorticotropic hormone, adrenomedullin (AM), aducanumab, acutumomab, afelimomab, afutuzumab, alacizumab pegol, alanine, albaconazole, alclofenac, alclometasone dipropionate, ALD518, aldosterone, alemtuzumab, algestonem, acetophenide, algestone, alirocumab, all-trans retinoic acid, allylestrenol, altrenogest, altumomab pentetate, amantadine, amatuximab, amcinonide, amfenac, amikacin, aminogluthethimide, aminoglycosides, aminophenazone, amorolfin, amoxicillin, amoxicillin/clavulanate, amphotericin B, ampicillin, ampicillin/sulbactam, ampiroxicam, ampligen, amprenavir, ampyrone, amsacrine, amtolmetin-guacil, amylin, anatumomab mafenatox, androgens (testosterone), anetumab ravtansine, angiopoietin (Ang), angiotensin, angiotensinogen, anidulafungin, anifrolumab, aniruzafem, anrukinzumab, antidiuretic hormone, anti-Müllerian hormone apolizumab, arbidol, arcitumomab, arginine, arsphenamine, ascrinvacumab, aselizumab, asparagine, aspartic acid, aspirin, astemizole, atazanavir, atezolizumab, atinumab, atlizumab, atorolimumab, atrial-natriuretic peptide,
atripla, autocrine motility factor, azacitidine, azapropazone, azathioprine, azelastine,
azithromycin, azlocillin, aztreonam, bacitracin, baicalein, balavir, bapineuzumab,
basiliximab, bavituximab, beclomethasone dipropionate, begolomab, belimumab, bendazac,
benorilate, benralizumab, benzoic acid, benzydamine, bertilimumab, besilesomab,
betamethasone, betamethasone dipropionate, betamethasone sodium phosphate,
betamethasone valerate, bevacizumab, bezlotoxumab, biciromab, bifenazole, bilastine,
bimagrumab, bimekizumab, bivatuzumab mertansine, bleomycin, blinatumomab,
blosozumab, bococizumab, bortezomib, brain natriuretic peptide, brain-derived neurotrophic
factor (BDNF), brentuximab vedotin, briakinumab, brodalumab, brolucizumab, bromfenac,
bromodiphenhydramine, brompheniramine, brotinctuzumab, buclizine, budenoside,
bumadizone, buserelin, busulfan, butenafine, butoconazole, caffeic acid, calcitonin,
canakinumab, candididin, canrenone, cantuzumab mertansine, cantuzumab ravtansine,
capecitabine, caplacizumab, capreomycin, capromab pendetide, carbapenems, carbenicillin,
carbinoxamine, carboplatin, carlumab, carmustine, carprofen, caspofungin, catechin,
catumaxomab, cBR96-doxorubicin immunoconjugate, cedelizumab, cefaclor, cefadroxil,
cefalexin, cefalotin, cefamandole, cefazolin, cefdinir, cefditoren, cefepime, cefixime,
cefoperazone, cefotaxime, cefoxitin, cefpodoxime, cefprozil, ceftaroline, ceftaroline fosamil,
ceftazidime, ceftazidime, cefituben, cefitoximex, ceftriaxone, cefuroxime,
celecoxib, certolizumab pegol, cetirizine, cetuximab, chlorambucil, chloramphenicol (Bs),
chloramadinone acetate, chlorodiphenhydramine, chlorotriamcinolone, chlorphenamine,
chlorpheniramine, chlorpromazine, cholecystokinin, ciclesonide, ciclopirox, cidofovir,
cimetidine, cimicoxib, ciprofloxacin, ciprofloxacin clemastine, cisplatin, citatuzumab bogatox,
cixutumumab, cladribine, clarithromycin, clazakizumab, clenoliximab, clindamycin,
clivatuzumab tetraxetan, clobenpropit, clobetasol-17-propionate, clobetasone-17-butyrate,
clofazimine, clofezone, clonixin, clotrimazole, cloxacillin, codrituzumab, colistin, coltuximab
ravtansine, combivir, conatumumab, concizumab, conessine, conjugate equine estrogen, copper ibuprofenate, corticosterone, corticotropin, corticotropin-releasing hormone, cortisone, cortistatin, CR6261, crenezumab, cromolyn sodium, curcumin, cyclizine, cyclophosphamide, cycloserine, cyproheptadine, cyproterone acetate, cysteine, cytarabine, dacarbazine, dacetuzumab, daclizumab, dactinomycin, dalbavancin, dalotuzumab, dapirolizumab pegol, dapsone, daptomycin, daratumumab, darunavir, daunorubicin, dextreki mumab, delavirdine, delmadinone acetate, demcizumab, demeclocycline, demegestone, dendrobine, denintuzumab mafodotin, denosumab, deracoxib, derlotuximab biotin, desbrompheniramine, deschlorpheniramine, desloratadine, desogestrel, desonide, dexamethasone sodium phosphate, dexamethasone, dexamethasone, dexibuprofen, dexketoprofen, diaziquone, diclofenac, diclofenac/misoprostol, dicloxacillin, didanosine, dienogest, diflunisal, dimenhydrinate, dimetindene, dinutuximab, diphenhydramine, dipyrrocetyl, diridavumab, dirithromycin, docetaxel, docosanol, dolutegravir, dopamine, doripenem, dorlimomab aritox, doxifluridine, doxorubicin, doxycycline, doxylamine, drosipe rone, droxicam, drozitumab, duligotumab, dupilumab, durvalumab, dusig tumab, dydrogesterone, ebastine, ecoliever, econazole, ecromeximab, eculizumab, ede bocom, edoxudine, edrecolomab, efalizumab, efavirenz, efinaconazole, efungumab, eldelumab, elgemtumab, elotuzumab, elsilimomab, emactuzumab, embramine, emibetuzumab, emtricitabine, enavatuzumab, endothelin, enfortumab vedotin, enfuvirtide, enkephalin, enlimomab pegol, enoblituzumab, enokizumab, entecavir, epidermal growth factor (EGF), epinephrine, epirizole, epirubicin, epitumomab cituxetan, epothilone, epoxiconazole, epratuzumab, erlizumab, ertapenem, ertumaxomab, erythromycin, erythropoietin (EPO), estramustine phosphate, estrogen, etaracizumab, ethambutol (Bs), ethenzamide, ethinyl estradiol, ethionamide, ethisterone, etodolac, etofenamate, etonogestrel, etoposide, etoricoxib, etrolizumab, etynodiol diacetate, evinacumab, evolocumab,
exbivirumab, famciclovir, famotidine, famprofazone, fanolesomab, faralimomab,
farletuzumab, fasinumab, FBTA05, felbinac, felvizumab, fenamic acid, fenbufen,
fenclofenac, fenclozic acid, fenoprofen, fenticonazole, feprazone, fexofenadine, fezakinumab,
fibroblast growth factor (FGF), ficlatuzumab, figitumumab, filipin, firivumab, firocoxib,
flanvotumab, fletikumab, floctafenine, floucortolone pivalate, floxuridine, fluocxacillin,
fluconazole, flucytosine, fludarabine, flunisolide, flunixin, fluocinolone acetonide,
fluocinonide, fluocortolone, fluocortolone caproate, fluoromethalone, fluoroquinolones,
fluorouracil, fluoxymesterone, fluprednidene acetate, fluroproquazone, fluridone,
flutamide, fluticasone furoate, fluticasone propionate, foetal bovine somatotrophin (FBS),
follicle-stimulating hormone, fomivirsen, fontolizumab, foralumab, foravirumab,
fosamprenavir, foscarin, fosfomycin, fosnet, fresolimumab, fulranumab, furazolidone,
fusidic acid, futuximab, galanin, galiximab, ganciclovir, ganitumab, gantenerumab,
gastric inhibitory polypeptide, gastrin, gatifloxacin, gavilimomab, geldanamycin, gemcitabine,
gepifloxacin, gemtuzumab ozogamicin, gentamicin, gestodene, gestonorone caproate,
gestrinone, gevokizumab, ghrelin, girentuximab, glafenine, glembatumumab vedotin, glial
cell line-derived neurotrophic factor (GDNF), glucagon, glucagon-like peptide-1,
glucocorticoids (Cortisol), glucuronate, glutamic acid, glutamine, glycine, golimumab,
gomiliximab, gonadotropin-releasing hormone, goserelin acetate, granulocyte colony-
stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF),
grepafloxacin, griseofulvin, growth differentiation factor-9 (GDF9), hepatocyte growth factor
(HGF), hepatoma-derived growth factor (HDGF), growth hormone, growth hormone-
releasing hormone, guselkumab, halcinonide, halometasone, haloprogesterone, haloprogin,
hamycin, hepcidin, herbimycin, histidine, human chorionic gonadotropin, human placental
lactogen, hydrocortisone, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate,
hydrocortisone-17-butyrate, hydrocortisone-17-valerate, hydroxyprogesterone acetate,
hydroxyprogesterone caproate, hydroxyprogesterone caproate, hydroxyprogesterone heptanoate, hydroxyurea, hydroxyzine, hyperforin, ibacitabine, ibalizumab, ibritumomab tiuxetan, ibuprofen, icrucumab, idarucizumab, idarubicin, idoxuridine, ifosfamide, igovomab, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IMAB362, imalumab, imatinib, irinotecan, imciromab, imatuzumab, imipenem/cilastatin, imiquimod, imunovir, inclacumab, indatuximab ravtansine, indinavir, indometacin farnesil, indometacin, indoprofen, indusatumab vedotin, infliximab, inhibin, inolimomab, inosine, inotuzumab ozogamicin, insulin, insulin-like growth factor (IGF), interferon, intetumumab, ipilimumab, iratumumab, isatuximab, isavuconazole, isoconazole, isoleucine, isoniazid, isoxicam, itolizumab, itraconazole, ixekizumab, JNJ-7777120, kanamycin, keliximab, keratinocyte growth factor (KGF), ketoconazole, ketofifen, ketoprofen,ketorolac, labetuzumab, latexitidine, lambrolizumab, lamivudine, lampalizumab, L-asparaginase, lebrikizumab, lemalesomab, lenzilumab, leptin, lerdelimumab, leucine, leukotrienes, leuprolide, levamisole, levocetirizine, levofloxacin,levonorgestrel, lexatumumab, libivirumab, licofelone, lifastuzumab vedotin, ligelizumab, lilotomab satetraxetan, lincomycin, linezolid, lintuzumab, lipotropin, lirilumab, lodolcizumab, lokivetmab, lomefloxacin, lomustine, lonazolac, lopinavir, loracarbef, lornotadine, loroxicam, lorvotuzumab mertansine, loviride, loxoprofen, lucatumumab, luliconazole, lulizumab pegol, lumiliximab, lumiracoxib, lumretuzumab, luteinizing hormone, lynestrenol, lysine, mafenide, magnesium salicylate, mapatumumab, maraviroc, margetuximab, maslimomab, matuzumab, mavacoxib, mavrilimumab, mechlorethamine, meclofenamate sodium, meclozine, medrogestone, medroxyprogesterone acetate, medroxyprogesterone, mefenamic acid, megestrol acetate, melanocyte stimulating hormone, melatonin, melengestrol acetate, meloxicam, melphalan, mepolizumab, mercaptopurine, meropenem, mesoclazone, metelimumab, methdilazine, methicillin, methionine, methisazone, methotrexate, methyl-GAG, methylprednisolone, metimazole,
metronidazole, mezlocillin, micafungin, miconazole, migration-stimulating factor (MSF),
milatuzumab, mineralocorticoids (aldosterone), minocycline, minretumomab, miprofen,
mirtazapine, mirvetuximab soravtansine, mitomycin, mitotane, mitoxantrone, mitumomab,
mizolastine, mofebutazone, mogamulizumab, mometasone, montelukast, morazone,
morolimumab, moroxydine, motavizumab, motilin, m oxetumomab pasudotox, moxifloxacin,
mupirocin, muromonab-CD3, myostatin (GDF-8), nabumetone, nacolomab tafenatox,
nafcinill, naftifine, nalidixic acid, namilumab, naproxinod, naprofen, naptumomab
estafenatox, narratumab, naturalizumab, natamycin, nebacumab, necitumumab, nedocromil,
nelfinavir, nemolizumab, neomycin, nepafenac, nerelimomab, nerve growth factor (NGF),
nestorone, nesvacumab, netilmicin, nevirapine, nexavir, nimesulide, nimotuzumab,
nitazoxanide, nitrofurantoin (B5), nivolumab, nizatidine, nofetumomab merpentan,
nomegestrol acetate, norelgestromine, norepinephrine, norethandrolone, norethisterone
(norethindrone), norethisterone acetate, norethisterone enanthate, noretynodrel, norfl oxacin,
norgestagon, norgestimate, norgestomet, norgestrel, norgestrienone, normethandron
(methylestrenolone), norvinisterone, NOSH-aspirin, novir, NS-398, nystatin, obiltoximab,
obinutuzumab, ocaratuzumab, ocrelizumab, odulimomab, ofatumumab, ofloxacin,
olaratumab, olo kizumab, olopadidine, omalizumab, omoconazole, onartuzumab,
onuxizumab, opicinumab, oportuzumab monatox, oregovomab, orexin, oritavancin,
orphenadrine, orticumab, oseltamivir, oteloxizumab, otlertuzumab, oxacillin, oxaliplatin,
oxaprozin, oxelumab, oxicam, oxiconazole, oxybenzacetone, oxytetracycline, oxytocin,
 oxyazumab, ozoralizumab, paclitaxel, pagibaximab, palivizumab, pancreatic panitumumab,
pankomab, panobacumab, parathyroid hormone, parecoxib, paromomycin, parsatuzumab,
pascolizumab, pasotuxizumab, pateclizumab, patritumab, peginterferon alfa-2a,
pembrolizumab, pemetrexed, pentumomab, penciclovir, penicillin G, penicillin V,
pentostatin, perakizumab, peramivir, pertuzumab, pexelizumab, phenazone, phenindamine,
pheniramine, phenylalanine, phenylbutazone, phenyltoloxamine, pibobroman, pidilizumab, pinatuzumab vedotin, pintumomab, pipercillin, pipercillin/tazobactam, piperylone, piroxicam, pirprofen, pituitary adenylate cyclase-activating peptide, Placental growth factor (PGF), placulumab, platelet-derived growth factor (PDGF), platensimycin, pleconaril, plicamycin, polatuzumab vedotin, polmacoxib, polymyxin B, ponezumab, posaconazole, posizolid, potassium canrenoate, pranlukast, pranoprofen, prednicarbate, prednisolone, prednisone, priliximab, pritoxaximab, pritumumab, PRO 140, procarbazine, progestosterone, progestogen, proglumetacin, prolactin releasing hormone, prolactin, proligestone, proline, promegestone, promethazine, propiconazole, propyphenazone, prostacyclin, prostaglandins, pyramidine, pyrazinamide, quetiapine, quilizumab, quingestanol acetate, quinupristin/dalfopristin, racotumomab, radezolid, radretumab, rafivirumab, ralpancizumab, raltegravir, ramucirumab, ranibizumab, ranitidine, rauconazole, raxibacumab, refanezumab, regavirumab, relaxin, renalase (RNLS), renin, reslizumab, ribavirin, rifabutin, rifampicin (rifampin), rifaximin, rilotumumab, rimantadine, rimocidin, rinucumab, ritonavir, rituximab, robatumumab, robenacoxib, rofecoxib, roledumab, romosozumab, rontalizumab, rovelizumab, roxatidine, roxithromycin, rupatadine, ruplizumab, sacituzumab govitecan, salicylamide, salicylic acid, salix alba, salmetrol xinafoate, salsalate, samalizumab, saquinavir, sarilumab, satumomab pendetide, secosteroid, secretin, secukinumab, semustine, seribantumab, serine, sertaconazole, setoximab, sevirumab, SGN-CD19A, SGN-CD33A, sibrotuzumab, sifalimumab, siltuximab, silver and silver salts, silver sulfadiazine, simtuzumab, sipilizumab, sirukumab, sofituzumab vedotin, sofosbuvir, solanezumab, solitomab, somatostatin, sonepcizumab, sontuzumab, sparfloxacin, spectinomycin (Bs), spiramycin, spironolactone, stamulumab, stavudine, streptogramins, streptomycin, streptozocin, sulconazole, sulesomab, sulfacetamide, sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole,
sulfonamidochrysoidine, sulindac, suprofen, suvizumab, tabalumab, tacatuzumab tetraxetan,
tadocizumab, talizumab, tamoxifen, tanezumab, taplitumomab paptax, tarenflurbil,
tarexatumab, T-cell growth factor (TCGF), tedizolid, tefibazumab, tegafur, teicoplanin,
teixobactin, telaprevir, telavancin, telimomab aritox, telithromycin, temafloxacin, temocillin,
tenatumomab, teneliximab, tenidap, teniposide, tenofovir, tenofovirdisoproxil, tenoxicam,
tepalumab, tepoxalin, teprotumumab, terbinafine, terfenadine, terconazole, tesidolumab,
testolactone, tetracycline, tetulomab, TGN1412, thiamphenicol, thioperamide, thiotepa,
thaonine, thrombopoietin (TPO), thromboxane, thymosins, thyroid-stimulating hormone,
thyrotropin-releasing hormone, thyroxine, tiaprofenic acid, tibolone, ticarcillin,
ticarcillin/clavulanate, ticilimumab, tigatumumab, tigecycline, tildrakizumab, tinidazole,
tioconazole, tioguanine, tiotidine, tipranavir, tixocortol, TNX-650, tobramycin, tocilizumab,
tolfenamic acid, tolmetin, tolnaftate, topotecan, toralizumab, torezolid, tosatoxumab,
tositumomab, tovetumab, tralokinumab, transforming growth factor alpha (TGF-a),
transforming growth factor beta (TGF-β), trastuzumab emtansine, trastuzumab, TRBS07,
tregalizumab, tremelimumab, trenbolone, trengestone, trevogrumab, triamcinolone,
triamcinolone acetonide, trifluridine, triiodothyronie, triiodothyronine, trimegestone,
dimethisterone, trimethazine, trimethoprim (B₃), trimethoprim-sulfamethoxazole,
trimetrexate, tripelennamine, tripipridine, tritoqualine, trizivir, troleandomycin, tromantadine,
trovafloxacin, truvada, tryptophan, tucotuzumab celmoleukin, tumor necrosis factor-alpha
(TNF-a), tuvirumab, tyrosine, ublituximab, ulocuplumab, undecylenic acid, uracil mustard,
urelumab, urtoxazumab, ustekinumab, valaciclovir, valdecoxib, valganciclovir, valine,
valrubcin, vancomycin, vandortuzumab vedotin, vantanctumab, vanucizumab, vapaximab,
varelumab, vascular endothelial growth factor (VEGF), vasoactive intestinal peptide,
vasopressin, vatalizumab, vedaprofen, vedolizumab, veltuzumab, vepalimomab, vesencumab,
vicriviroc, vidarabine, vimovo, vinblastine, vincristine, vindesine, vinorelbine, viramidine,
visilizumab, volociximab, voriconazole, vorsetuzumab mafodotin, votumumab, VUF-6002,
Want signaling pathway polypeptides, xylometazoline, zafirlukast, zalcitabine, zalutumumab,
zanamivir, zanolimumab, zatuximab, zidovudine, zileuton, ziralimumab, zolimomab aritox,
zomepirac,

[0047] Other biologically active agents that may be incorporated into and/or onto the coating of the presently disclosed implantable medical devices include, but are not limited to, aptamers, humoral agents, osteoinductive agents, osteoinductive agents, pro-osteogenic compounds. Examples of aptamer nucleotides can be found in the searchable GenBank nucleotide database maintained by the National Center for Biotechnology Information, which can be accessed at http://www.ncbi.nlm.nih.gov/nuccore. Examples of humoral agents include, but are not limited to, alexins, complement proteins (e.g., C3b, C4b, and Clq), antitoxins, bacteriolysins, bacterial agglutinins, bacterial precipitins, hemolysins, opsonins, such as pentraxins (e.g., C-reactive protein (CRP), serum amyloid P component protein (SAP), female protein (FP), neural pentraxin I (NPTXI), and neural pentraxin II (NPTXII)), collectins (e.g., mannan-binding lectin (MBL), surfactant protein A (SP-A), surfactant protein-D (SP-D), collectin liver 1 (CL-L1), collectin placenta 1 (CL-P1), conglutin collectin of 43 kDa (CL-43), collectin of 46 kDa (CL-46), collectin kidney 1 (CL-K1), and conglutinin), and ficolins (e.g., FCN1, FCN2, and FCN3). Examples of osteoconductive agents include, but are not limited to, calcium hydroxyapatite, hydroxyapatite, icariin, monocalcium phosphate, dicalcium phosphate, a-tricalcium phosphate (a-TCP), β-tricalcium phosphate (β-TCP), octacalcium phosphate, tetracalcium phosphate, dicalcium phosphate, fluoroapatite, calcium sulphate, calcium fluoride, calcium oxide, calcium phosphate apatites, such as Ca₅(PO₄)(OH)₂OH, Ca₅(PO₄)₃OH, and Ca₁₀(PO₄)₆O, and non-calcium phosphate apatites, such as Ba₅(P0₄)₃Cl, (Sr,Ce)₅(PO₄)₃OH, (Ce,Ca)₅(P0₄)₃(OH,F),
(Y,Ca)$_5$(IO$_4$)$_3$(OH,F), Na$_3$Pb$_3$(SO-0 3Cl, Na$_3$XV$_4$(SO$_4$)$_2$OH, Ca$_3$(Si0$_4$), PO$_4$S$_G$-0 3(CL,F),
Pb$_5$(AsO-0 3Cl, (Ca,Sr)$_5$(AsO$_4$)$_5$OH, Pb(As0$_4$)$_3$Cl, Ca$_3$(Si0$_4$)P0$_4$S$_O_3$(F,OH,Cl),
Pb$_3$Ca$_2$(AsO-0 3Cl, Ca$_3$(Si0$_4$)P0$_4$S$_O_3$(OH, Cl), Ca$_3$(As0$_4$)$_3$(OH, Pb$_5$(As0$_4$)$_3$Cl,
(Ba,Ca,Pb)$_5$(As04$_4$)Q$_2$Q$_1$, Pb$_3$(PO-0 3Cl, Sr$_3$(P0$_4$)$_2$(C)H,F), Ca$_3$(As0$_4$)$_3$F,
Ca$_5$(As0$_4$)P0$_4$3Cl, and P$_S^4$(OCl)Cl. Examples of osteoinductive agents include, but are not
limited to, bone morphogenetic protein (BMP), such as BMP- 1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-15, BMP-16, BMP-17, BMP-18, BMP-19, and BMP-20 including full length BMPs or fragments
to thereof, vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF),
osteoprotegerin, growth differentiation factors (GDFs), cartilage derived morphogenic
proteins (CDMPs), lim mineralization proteins (LMPs), platelet derived growth factor,
(PDGF), insulin-like growth factor (IGF), and transforming growth factor beta (TGF-beta)
proteins. Examples of pro-osteogenic compounds include, but are not limited to, alpha-lipoic
acid, cytochalason D, GSK126, sulforothane, methylsulfonylethane, erucin, hydrogen
sulfide, iberin, and allyl isothiocyanate.

[0048] The biologically active agents can be incorporated into and/or onto the coating
of the presently disclosed implantable medical devices by any known means. In certain
embodiments, the biologically active agents are covalently bonded to functional groups in
and/or on the coating. The biologically active agent can be covalently bonded to a functional
group located in and/or on the coating either directly or via a linker. In embodiments where
the functional group in and/or on the coating is a hydroxyl group, the biologically active
agent comprises at least one functional group capable of reacting with a hydroxyl group. In
embodiments where the biologically active agent is covalently bonded to the coating via a
linker, any known biocompatible precursor molecule having at least one functional group that
can covalently bond to a functional group in and/or on the coating and at least one functional group that can covalently bond to a functional group on the biologically active agent can be used as the linker. In certain embodiments, the linker precursor molecule is first reacted with a functional group in and/or on the coating. The biologically active agent is then subsequently reacted with the coating-bound linker precursor. In certain other embodiments, the linker precursor molecule is first reacted with the biologically active agent. The linker precursor now attached to the biologically active agent is then subsequently reacted with a functional group in and/or on the coating. In embodiments where the functional group in or on the coating is a hydroxyl group, the linker precursor molecule has at least one functional group capable of reacting with a hydroxyl group and at least one functional group capable of reacting with a functional group on the biologically active agent. In certain other embodiments, the biologically active agent is non-covalently associated to the coating. As used herein, the term "non-covalently associated" encompasses any kind of intermolecular interaction between the biologically active agent and the coating other than covalent interactions (i.e., interactions that involve the sharing of electrons). Examples of such non-covalent interactions include, but are not limited to, electrostatic interactions, such as ionic interactions, hydrogen bonding, and halogen bonding, Van der Waals forces, such as the Keesom force, the Debye force, and London dispersion forces, \( \pi \)-effects, such as \( \pi \)-\( \pi \) interactions, cation-\( \pi \) interactions, anion-\( \pi \) interactions, and polar \( \pi \) interactions, and hydrophobic interactions. In certain embodiments, the coating comprises functional groups capable of forming hydrogen bonds, such as hydroxyl, amino, and carboxylate groups. In certain embodiments, the coating comprises hydroxyl groups, the biologically active agent comprises one or more functional groups capable of acting as hydrogen-bond acceptors, and the biologically active agent is non-covalently associated to the coating via hydrogen bonds
between the hydroxyl groups of the coating and the hydrogen bond acceptors of the biologically active agent.

[0049] The present invention is further illustrated and described in the following Examples. It should be understood that these Examples, while indicating exemplary embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

EXAMPLE

[0050] General Procedure for Manufacturing a Bearing Head Having a Hydrophilic Surface:

[0051] First, a bearing head is machined or 3-dimensionally (3D) printed from Ti-6Al-4V alloy as the base material. The bearing head is then heat-treated to relieve residual stress. Next, the bearing head is then machined to incorporate a female trunnion so as to enable intraoperative assembly of the bearing head onto an intramedullary fixation stem, such as a femoral hip stem or humeral shoulder stem. The surface of the bearing head is then prepared for application of the Ti$_x$Al$_{1-x}$N ceramic coating by polishing or etching. A Ti$_x$Al$_{1-x}$N ceramic coating is then applied having a total thickness in the range of from 0.5 to 20.0 microns, with or without intermediate layer(s) of bond coating(s) or other ceramic species. The coated bearing head is then treated with steam or aqueous hydroxide solution in an autoclave or, alternatively, is treated with an acid to introduce micropores and/or nanopores into the coating.
CLAIMS

1. An implantable medical device comprising a base material that defines a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and one or more layers, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits increased hydrophilicity relative to the hydrophilicity of the at least a portion of the coating prior to modification.

2. The implantable medical device of claim 1, wherein the coating comprises a surface layer and at least one intermediate layer disposed between the surface layer and the surface of the base material.

3. The implantable medical device of claim 2, wherein the coating comprises from 1 to 12 intermediate layers.

4. The implantable medical device of claim 2, wherein at least one intermediate layer is a bonding layer.

5. The implantable medical device of claim 4, wherein the bonding layer of the coating interfaces with the surface of the base material.

6. The implantable medical device of claim 1, wherein the hydrophilic portion of the coating comprises hydroxyl groups.

7. The implantable medical device of claim 1, wherein the hydrophilic portion of the coating comprises oxide groups.
8. The implantable medical device of claim 1, wherein the hydrophilic portion of the coating comprises micropores, nanopores, etches, surface texturing/patterning, and/or dimples.

9. The implantable medical device of claim 1, wherein the base material comprises a material selected from the group consisting of metals, metal alloys, ceramics, polymers, silicon-based compounds, metal matrix composites, ceramic matrix composites, polymer matrix composites, and combinations thereof.

10. The implantable medical device of claim 9, wherein the base material comprises a metal selected from the group consisting of titanium, titanium alloys, cobalt, cobalt alloys, cobalt-chromium alloys, tantalum, tantalum alloys, niobium, niobium alloys, zirconium, zirconium alloys, stainless steel, and combinations thereof.

11. The implantable medical device of claim 10, wherein the metal further comprises a dopant.

12. The implantable medical device of claim 11, wherein the dopant is selected from the group consisting of alkaline earth metals, transition metals, rare earth elements, and combinations thereof.

13. The implantable medical device of claim 12, wherein the dopant is selected from the group consisting of calcium, magnesium, strontium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, zirconium, and niobium.

14. The implantable medical device of claim 9, wherein the base material comprises a polymer selected from the group consisting of ultrahigh molecular weight polyethylene,
polyethylene oxide, polypropylene, polytetrafluoroethylene, polylactic acid, polyglycol acid, copolymers of polylactic acid and polyglycol acid, and combinations thereof.

15. The implantable medical device of claim 9, wherein the base material comprises a ceramic of formula (I):

\[ [(M_1)_a(M_2)_b(M_3)_c]x[(0)_d(C)e(N)f]^{(i-x)} \]  

(1)

wherein

- \( M_1, M_2, \) and \( M_3 \)
  - are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B;
- O is oxygen;
- C is carbon;
- N is nitrogen;
- \( a, b, c, d, e, \) and \( f \)
  - are each a number in the range of from 0 to 1, with the proviso that the sum of \( a, b, \) and \( c \) is equal to 1 and the sum of \( d, e, \) and \( f \) is equal to 1; and
- \( x \)
  - is a number greater than 0 and less than 1.

16. The implantable medical device of claim 15, wherein the base material comprises a ceramic selected from the group consisting of titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium
carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof.

17. The implantable medical device of claim 1, wherein the coating comprises a material selected from the group consisting of ceramics, metals, metal alloys, and combinations thereof.

18. The implantable medical device of claim 17, wherein the coating comprises a ceramic of formula (I):

\[((M_i)_{a} (M_2)_{b} (M_3)_{c})x (0)_{d} (C)_{e} (N)_{f}(i-x)\]  \hspace{1cm} (I)

wherein

- $M_i$, $M_2$, and $M_3$ are each, independently, selected from the group consisting of Ti, Zr, Al, Cr, Nb, Ta, Hf, Si, and B;
- O is oxygen;
- C is carbon;
- N is nitrogen;
- $a$, $b$, $c$, $d$, $e$, and $f$ are each a number in the range of from 0 to 1, with the proviso that the sum of $a$, $b$, and $c$ is equal to 1 and the sum of $d$, $e$, and $f$ is equal to 1; and
x is a number greater than 0 and less than 1.

19. The implantable medical device of claim 18, wherein the coating comprises a ceramic selected from the group consisting of titanium carbides, titanium nitrides, titanium oxynitrides, titanium carbonitrides, titanium aluminum nitrides, titanium niobium nitrides, titanium chromium nitrides, titanium zirconium nitrides, titanium silicon nitrides, titanium aluminum silicon nitrides, titanium aluminum chromium nitrides, titanium niobium carbides, titanium chromium carbides, titanium zirconium carbides, titanium aluminum carbides, titanium boron carbonitrides, titanium aluminum carbonitrides, zirconium oxides, zirconium carbides, zirconium nitrides, zirconium aluminum nitrides, zirconium aluminum carbides, zirconium titanium carbides, aluminum nitrides, aluminum carbides, aluminum oxides, aluminum titanium nitrides, aluminum chromium nitrides, aluminum zirconium nitrides, aluminum zirconium carbides, silicon nitrides, silicon oxides, silicon oxycarbonitrides, chromium nitrides, chromium carbides, chromium carbonitrides, chromium aluminum nitrides, niobium carbides, and combinations thereof.

20. The implantable medical device of claim 1, wherein the coating has a thickness in the range of from 0.5 µm to 20 µm.

21. The implantable medical device of claim 1, wherein the coating has been applied to the surface of the base material via physical vapor deposition (PVD), cathodic arc PVD, steered cathodic arc PVD, filtered cathodic arc PVD, plasma-assisted PVD, laser-assisted PVD, DC magnetron sputtering, RF magnetron sputtering, unbalanced magnetron sputtering, high power impulse magnetron sputtering, chemical vapor deposition (CVD), plasma-assisted CVD, laser-assisted CVD, plasma-enhanced CVD, photo-enhanced CVD, metal-organic CVD, atmospheric pressure CVD, ion plating, pulsed laser deposition, atomic laser
deposition, cold spray, thermal spray, solution plasma spray, solution precursor plasma spray, plating, reactive evaporation, reactive ion beam assisted deposition, and combinations or hybrid techniques thereof.

22. The implantable medical device of claim 1, wherein a biologically active agent is incorporated into the coating, onto the coating or a combination thereof.

23. The implantable medical device of claim 22, wherein the biologically active agent is hydrogen bonded to the coating.

24. The implantable medical device of claim 23, wherein the biologically active agent is hydrogen bonded to the coating via one or more hydroxyl groups.

25. The implantable medical device of claim 22, wherein the biologically active agent is covalently bonded to the coating.

26. The implantable medical device of claim 25, wherein the biologically active agent is covalently bonded to the coating via one or more hydroxyl groups.

27. The implantable medical device of claim 22, wherein the biologically active agent is selected from the group consisting of proteins, peptides, aptamers, standard and non-standard amino acids, lipids, lipopolysaccharides, growth factors, cytostatic agents, hormones, antibiotics, anti-microbial agents, anti-allergenic agents, steroidal and non-steroidal anti-inflammatory agents, progestational agents, humoral agents, antipyretic agents, osteoinductive agents, osteoconductive agents, pro-osteogenic compounds, and combinations thereof.

28. The implantable medical device of claim 1, wherein the implantable medical device is an orthopedic implantable medical device.
29. The implantable medical device of claim 28, wherein the orthopedic implantable medical device is selected from the group consisting of bone caps, plates, cerclages, rods, dowels, pegs, smooth fasteners, threaded fasteners, screws, staples, nails, washers, nuts, bolts, clamps, fixation orthoses, pedicle screw systems, intervertebral body fusion devices, ankle joint prostheses, elbow joint prostheses, hinged elbow fixators, finger joint prostheses, hip joint prostheses, knee joint femorotibial prostheses, knee joint patellofemoral prostheses, knee joint patellofemorotibial prostheses, knee joint femoral prostheses, knee joint patellar prostheses, knee joint tibial prostheses, shoulder joint prostheses, wrist joint prostheses, maxillofacial prostheses, cranial prostheses, pelvic fixators, cranial distractors, transmandibular implants, mandibular fixators and distractors, preformed cement bone replacements, polymer bone replacements, and orthodontic prostheses.

30. The implantable medical device of claim 1, wherein the base material of the orthopedic implantable medical device comprises titanium metal or an alloy thereof.

31. The implantable medical device of claim 30, wherein the coating comprises at least one layer comprising a ceramic of formula (II):

\[ \text{Ti}_x\text{Al}_{(1-x)}\text{N} \] (II)

wherein

\[ x \] is a number greater than 0 and less than 1.

32. The implantable medical device of claim 31, wherein the at least one layer comprising a ceramic of formula (II) has an aluminum concentration of up to 80 % by weight.

33. The implantable medical device of claim 31, wherein the concentration of aluminum in the at least one layer comprising a ceramic of formula (II) increases in a gradient from the
surface of the at least one layer disposed closest to the surface of the base material to the surface of the at least one layer disposed furthest from the surface of the base material.

34. The implantable medical device of claim 31, wherein the coating is located on a surface of the orthopedic implantable medical device that interfaces with bone.

35. The implantable medical device of claim 31, wherein the coating is located on a surface of the orthopedic implantable medical device that forms an articulating interface when implanted.

36. The implantable medical device of claim 31, wherein the orthopedic implantable medical device is a hip joint prosthesis having a femoral head and the coating is located on the femoral head.

37. The implantable medical device of claim 31, wherein the coating is located on the surface of the implantable medical device that attaches to or interfaces with tissue when implanted.

38. The implantable medical device of claim 1, wherein the implantable medical device is a non-orthopedic medical device.

39. The implantable medical device of claim 38, wherein the non-orthopedic implant is selected from the group consisting of cardiac pacemakers, heart valve rotators, esophageal prostheses, smooth fasteners, threaded fasteners, sacculotomy tacks, clips, nerve stimulators, ocular orbital implants, shunts and shunt tubes, fistula adapters, cardiac event recorders, stents, ports, tympanostomy tubes, eyelid weights, prostate magnetic and thermal rod systems, surgical meshes, tracheostomy tubes and tube cuffs, tracheal prostheses, in utero fetal tracheal occlusion devices, tongue suspension systems, defibrillators, ionizing radiation systems, surgical meshes, tracheostomy tubes and tube cuffs, tracheal prostheses, in utero fetal tracheal occlusion devices, tongue suspension systems, defibrillators, ionizing radiation systems,
dosimeters, radio frequency transponder systems, aneurysm pressure sensors, catheters, uterine implants, mitral valve prostheses, hearing aids, and orbital tissue expanders.

40. An implantable medical device comprising a base material that defines a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and at least one layer, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits a decreased coefficient of friction relative to the coefficient of friction of the at least a portion of the coating prior to modification.

41. The implantable medical device of claim 40, wherein the coefficient of friction of the coating is decreased by 0.001 to 99.999%, relative to the coefficient of friction of the coating prior to modification.

42. The implantable medical device of claim 1, wherein the hydrophilicity of the coating is increased by 0.001 to 1000%, relative to the hydrophilicity of the coating prior to modification.

43. The implantable medical device of claim 40, wherein at least a portion of the coating is modified by (1) exposing the coating to ozone, (2) exposing the coating to water or steam at a temperature above ambient temperature, (3) exposing the coating to a basic solution at a temperature above ambient temperature, or (4) altering the surface morphology of the coating and optionally coating the morphologically altered coating with a polymer or wax, or (5) any combination thereof.

44. The implantable medical device of claim 43, wherein the exposure of (1), (2), (3) and (4) is conducted for a time period in the range of from 1 minute to 168 hours.
45. The implantable medical device of claim 43, wherein the exposure of (1), (2), (3) and (4) is conducted at a pressure above atmospheric pressure.

46. The implantable medical device of claim 43, wherein the basic solution is selected from the group consisting of aqueous solutions comprising NaOH, aqueous solutions comprising KOH, aqueous solutions comprising Ca(OH)₂, aqueous solutions comprising Mg(OH)₂, and any combination thereof.

47. An implantable medical device comprising a base material that defines a surface, wherein at least a portion of the surface of the base material comprises a coating comprising a top surface and a bottom surface and at least one layer, wherein the bottom surface interfaces with the surface of the base material and at least a portion of the coating has been modified such that it exhibits increased bone affinity and attachment relative to the bone affinity and attachment of the at least a portion of the coating prior to modification.

48. The implantable medical device according to any of the preceding claims, wherein the coating is located on a surface of the orthopedic implantable medical device that forms an articulating interface when implanted.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61 L 27/28; A61 L 27/30; A61 M 31/00 (2017.01)
CPC - A61 L 27/28; A61 L 27/30; A61 L 27/303; A61 L 27/306; A61 M 31/002 (2017.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search: 04 December 2017
Date of mailing of the international search report: 26 DEC 2017

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